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Rodrigo-Troyano, Ana; Suarez-Cuartin, Guillermo; Peiró, Meritxell; Barril, Silvia; Castillo, Diego; Sanchez-Reus, Ferran

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# *Pseudomonas aeruginosa* resistance patterns and clinical outcomes in hospitalized exacerbations of COPD

Ana Rodrigo-Troyano [1,2], Guillermo Suarez-Cuartin [1,2], Meritxell Peiró[1,2], Silvia Barril[1,2], Diego Castillo [1,2], Ferran Sanchez-Reus [2,3], Vicente Plaza [1,2], Marcos I Restrepo[4], James D Chalmers[5], Oriol Sibila[1,2]

[1]Servei de Pneumologia, Hospital de la Santa Creu i Sant Pau, Universitat Autonoma de Barcelona, Barcelona, Spain; [2]Institut d´Investigació Biomèdica Sant Pau (IIB Sant Pau); [3]Servei de Microbiologia, Hospital de la Santa Creu i Sant Pau, Universitat Autónomoa de Barcelona, Barcelona, Spain; [4]South Texas Veterans Health Care System and University of Texas Health Science Center at San Antonio, San Antonio, TX [5]Tayside Respiratory Research Group, University of Dundee, Dundee, UK.

**Corresponding author**: Dr. Oriol Sibila. Servei de Pneumologia, Hospital de la Santa Creu i Sant Pau. C/. Sant Antoni M. Claret 167, 08025 Barcelona (Spain). Tel.: +34 93 556 5964; Fax: +34 93 556 5601. E-mail: osibila@santpau.cat

**ABSTRACT**

Introduction: Acute exacerbations of Chronic Obstructive Pulmonary disease (AECOPD) due to *Pseudomonas aeruginosa* (PA) are associated with worse outcomes. PA antibiotic resistance is important to determine treatment and may influence clinical outcomes.

Objectives: To study clinical characteristics and outcomes in patients with AECOPD associated with PA based on their antibiotic resistance.

Methods: Prospective observational study including all patients with AECOPD and positive PA sputum culture admitted in a Respiratory ward in a tertiary hospital in Barcelona during 2013-2014. PA was defined as Resistant (PA-R) when the antibiogram showed ≥1 resistance.

Results: 401 patients with AECOPD were evaluated. Of them, 54 (13 %) had a positive PA sputum culture. 82% were men, median age 77 (SD 7) years old and FEV1 36 (SD 17) % of predicted. PA-R was isolated in 35 patients (66%) and PA-Sensitive (PA-S) was isolated in 18 (34%) patients. No differences were found in demographics, lung function and comorbidities among groups. PA-R patients were more likely exposed to prior oral corticosteroids (77% vs. 44%, p = 0.03) and antibiotics (77% vs. 31%, p = 0.01), respectively. AECOPD patients associated with PA-S were more likely to died at 30-days (Odds Ratio (OR) 13.53, 95% confidence interval (1.14-69.56, p=0.03) and 90-days (OR 7.09, 95%IC 1.33-37.89, p=0.02), respectively.

Conclusions: PA-R affects patients with severe ACOPD and previous use of corticosteroids and antibiotics. The presence of PA-S is associated with higher mortality. These results may suggest increased virulence in PA-S strains causing acute infections.

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**Key words:** *Pseudomonas aeruginosa*, COPD, Exacerbations

**Short title:** Sensitive *Pseudomonas aeruginosa* in COPD

**Summary at a glance:**

Pseudomonas aeruginosa (PA) plays an important role in AECOPD. Howere, the impact of PA resistance patterns in clinical outcomes is not clear. Our study demonstrates that the presence of sensitive-PA is associated with higher mortality

**Role of authors:**

All authors have given their final approval of the manuscript.

ART contributed to the study design, data acquisition, analysis and interpretation of the data, preparation of the manuscript and critical revision of the manuscript.

GSC contributed to the acquisition, analysis and interpretation of the data and preparation of the manuscript.

MP contributed to the acquisition, analysis and interpretation of the data and preparation of the manuscript.

SV contributed to the acquisition and interpretation of the data and preparation of the manuscript.

DC contributed to the acquisition and interpretation of the data, and critical revision of the manuscript.

FSR contributed to the analysis, interpretation of the data and preparation of the manuscript.

VP contributed to the analysis, interpretation of the data and critical revision of the manuscript

MIR contributed to the interpretation of the data and critical revison of the manuscript.

JDC contributed to the interpretation of the data and critical revison of the manuscript.

OS is the guarantor of the study, he coordinated all the steps including study design, obtaining funding, coordination acquisition of data, and preparation of the manuscript. OS had full access to the data and will vouch for the integrity of the data analysis

## INTRODUCTION

Acute exacerbations are the most important cause of hospital admission and mortality in patients with Chronic Obstructive Pulmonary Disease (AECOPD). Approximately 70% of these exacerbations are caused by respiratory infections, most of them due to bacteria [1;2]. *Pseudomonas aeruginosa* (PA) accounts for 5-30% of these bacterial exacerbations [1;3-5] and its presence was associated with worse clinical outcomes [6;7].

One of the features of PA is its capacity to generate resistance patterns against broad-spectrum antibiotics [8;9]. In recent years, the number of PA resistant strains has increased dramatically, limiting the likelihood of selecting antibiotics that adequately cover this microorganism [10]. Several studies in patients with bacteremia due to PA from different sources showed that antimicrobial resistance was related to severe adverse clinical outcomes [11-14]. A recent retrospective multicenter study of PA nosocomial pneumonia demonstrated that the presence of a multi-drug resistant (MDR) strain is associated with increased mortality [15]. In COPD, a case-control study showed that patients infected with MDR PA had a higher mortality compared to controls infected with non-MDR pathogens [16]. However, limited data are available regarding the impact of PA resistance patterns on clinical outcomes in exacerbations of COPD due to PA [17]. Patients with severe COPD are often chronically colonized with PA, where resistant PA may be a marker of longstanding PA colonization. During adaptation to chronic infection PA downregulates numerous virulence factors including a reduction in invasiveness, protease production and secretion of toxins [18]. This may

therefore suggest a counter-intuitive conclusion, that the presence of PA-R may be a marker of better outcome in AECOPD.

Therefore, the aim of this study was to characterize the impact of PA resistance patterns on clinical outcomes in COPD patients hospitalized due to an exacerbation

## METHODS

We conducted a prospective observational study in the Hospital de la Santa Creu i Sant Pau, Barcelona from January 1, 2013 to December 31, 2014. The study was approved by institutional review board (IIBSP-0921). Written consent was waived because of the non-interventional design.

### Subjects

Inclusion criteria were primary diagnosis of exacerbation of COPD and PA isolated in sputum culture during first 72 hours of admission. AECOPD was defined as an acute event characterized by a worsening of the patient´s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medications requiring hospitalization [19]. Diagnosis of COPD was confirmed by spirometry with baseline post-bronchodilator FEV1/FVC ratio <0.7 in all cases.

Exclusion criteria were airway disease primarily due to other cause (bronchiectasis, asthma, pneumonia, Interstitial lung disease) and patients in whom active treatment was not considered appropriate at admission (palliative care).

**Data collection**

Demographic data, clinical signs including Anthonisen criteria (ref), comorbid conditions, current treatments, smoking history, prior isolation of PA, number of hospitalizations for COPD within the last year and use of antibiotics and systemic corticosteroids within the last 3 months were recorded in all patients.

Clinical signs, laboratory tests and radiology results were assessed at the time of hospital admission. Antimicrobial treatment on admission and changes during the hospitalization were also collected.

**Microbiological evaluation**

Spontaneous sputum samples were collected in all patients during the first 72 hours of admission. Samples were submitted to the laboratory and processed immediately. Quality of specimens was determined microscopically according to the relative number of polymorphonuclear leukocytes and squamous epithelial cells (Bartlett RC, 1974). Samples with a Q-score of 0 or less were not processed. Potential pathogens were worked up using the Q234 score (Sharp S, 2004). All samples were processed, incubated and cultured as we previously described (ref). Antimicrobial susceptibility tests were performed using disk diffusion or microdilution methods according to guidelines and breakpoints established by the Clinical Laboratory Standards Insitute, Wayne, PA (CLSI) [20] . Sputum control samples were collected after finished antibiotic treatment in those clinically stable patients with sputum production.

**Commented [os1]:** Anthonisen NR, Manfreda J, Warren CPW. Antibiotic therapy... Ann intern Medf 1987

**Commented [os2]:** *Bartlett RC, 1974. Medical microbiology: quality costs and clinical relevance. John Wiley & Sons, Inc. New York, N.Y*

**Commented [os3]:** *Sharp S, 2004 Controversies in the performance of wound cultures. University of Texas Health Science Center Teleconference. Houston, Texas*

**Commented [os4]:** Garcia-Bellmunt L, Sibila o, "Nocardiosis...". Arch Bronconeumol 2012

To be classified as PA-R, the PA isolated in the sputum culture had to be non-susceptible to at least one of the following antimicrobial categories: antipseudomonal quinolones, antipseudomonal cephalosporins, antipseudomonal penicillins plus beta-lactamase inhibitors, antipseudomonal carbapenems, aminoglycosides, monobactams and polymixins. To be classified as Multi-Drug Resistant (MDR), the PA isolated had to be non-susceptible to one or more agents in three or more of the aforementioned antimicrobial categories [21].

Antimicrobial treatment was considered appropriate if at least one of the prescribed antibiotics was active against the identified PA isolated in the sputum based on its *in vitro* susceptibility [22].

**Outcomes**

The primary outcomes were 30-day and 90-day mortality (analysed as death from all causes from the first day of admission to completion 90 days of follow -up).

Secondary outcomes were length of hospital stay (LOS), intensive care unit (ICU) admission, need of non-invasive ventilation (NIV), need of mechanical ventilation (MV) and persistence of PA in sputum at 90 days. LOS was calculated as the date of discharge minus the date of admission. Persistence of PA was defined as a new positive PA sputum culture after at least 10 days of appropriate antibiotic treatment.

**Statistical analysis**

Univariate statistics were used to test the association of demographic and clinical characteristics with the presence of antimicrobial resistance. Categorical variables were analyzed using the Chi-square test and the continuous variables were analyzed using Student t test. We defined statistical significance as a two-tailed $p<0.05$

We performed logistic regression analyses using 30-day and 90-day mortality as dependent variables and PA-S as independent variable. Variables with $p<0.1$ in the univariate analyses (prior use of systemic steroids and antibiotics) were included in the multivariate analyses as potential cofounders. We also present a Kaplan-Meier curve representing the survival data. A secondary analysis was performed including only patients with PAR (MDR vs. not-MDR). All analyses were performed with SPSS 19.0 software program (SPSS Inc, Chicago, IL, USA).

**RESULTS**

During the study period, 401 patients were hospitalized with a primary diagnosis of AECOPD. PA was isolated from sputum samples obtained within 72 hours of hospitalization in 54 (13%) patients. The majority of the patients with AECOPD with PA in the sputum were man (n=48% [88%]), the median age (± SD) was 76 (± 7) years old, the median $FEV_1$ was 36 (± 17) % of predicted value and 8 (15%) were current smokers. Hypertension (64%) was the most common comorbid condition, and bronchiectasis (related to COPD) were present in 20% of the patients. Sputum purulence were present in 39 patients (72%) and median Anthoniesen criteria (± SD) were 2.2 (±0.5) suggesting an acute infectious exacerbation. 9 (16%) of the patients died before 90 days of

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follow-up. In all cases, respiratory failure was considered the cause of death. Most of the patients with confirmed PA-AECOPD had resistance to at least one antimicrobial category (PA-R, n=36 patients [66%]) and only one third (n=18 [33%]) of the patients had a sensitive PA (PA-S).

**1) Patient characteristics**

**Table 1** shows the characteristics of the subjects, grouped by whether they had PA-R or PA-S in the sputum. There were no statistical significant differences in gender, age, smoking status, lung function tests, pre-existing comorbid conditions, prior hospital, ICU and health-care admissions, clinical signs, laboratory tests and prior medications used among groups. However, PA-R patients were more likely to received prior systemic corticosteroids (77% vs. 44%, p=0.03) and prior antibiotics (77% vs 33%, p=0.01). AECOPD patients with evidence of prior (12 months) PA sputum isolation had a trend towards higher rates of PA-R compared to PA-S group (50% vs 22%, p=0.05).

Antibiotic treatment was similar in both groups (p=0.2). Cefepime (32%) and levofloxacin (30%) were the most common antibiotic used. Median days (±SD) were 12.5 ± 2.4 in the PA-R group and 13.7 ± 2.1 in the PA-S group (p=0.08). Initial antibiotic empiric treatment was appropriate in 12/18 (66%) of patients in the PAS group and 23/36 (63%) patients (p=0.7). Based on the results of antimicrobial susceptibility tests, antibiotic treatment was changed in 6 patients (33%) in the PA-S group and in 13 patients (36%) in the PA-R group and (p=0.8). Monotherapy was used in 27 patients (75%) with PA-R and in 16 patients (88%) with PA-S (p=0.2).

**2) Outcomes.**

**Table 2** shows clinical outcomes evaluated according PA antimicrobial resistance patterns. Patients with PA-S had higher 30-day (Odds Ratio (OR) 13.53, 95% confidence interval (95CI) 1.14-69.56, p= 0.03) and 90-day mortality (OR 7.09, 95%IC 1.33-37.89, p= 0.02) in the multivariate analyses. **Figure 1** shows the survival curves. Patients with PA-S had a longer hospital LOS (19.3 vs. 12.9 days, p=0.01). There were no differences on the rate of ICU admission and need for non-invasive or invasive mechanical ventilation.

However, in those patients who had received appropriate antibiotic treatment and control sputum was performed (n=38), persistence of PA was higher in the PA-R group compared to the PA-S group (50 vs. 83%, p=0.04).

**3) Subgroup analysis**

In order to assess the influence of MDR resistance pattern, we performed an additional analysis including only patients with PA-R (n=36). Of them, 17 patients (47%) had PA strains resistant to less than 3 different antibiotics classes (no MDR) and 19 (53%) had PA strains resistant to 3 or more different antibiotics classes (MDR).

There were no differences in the baseline characteristics among PA-R not-MDR and MDR, except that not-MDR had a higher rate of prior malignancy (47% vs 15%, p= 0.04) (**Table 3**). In addition, there were no statistical significant differences in the primary and secondary clinical outcomes among patients stratified according to the MDR status (**Table 4**). Persistence of PA was higher in the MDR group (87% vs 75%), although differences were not statistically significant (p=0.7).

## DISCUSSION

The main findings of our study are that COPD patients hospitalized with an exacerbation due to PA-S have higher 30-day and 90-day mortality compared to those with PA-R. However, the persistence of PA in the sputum after a proper antibiotic treatment was higher in those patients with PA-R. This suggests an important difference in the virulence characteristics of sensitive and resistant isolates in this population.

Infection with PA plays an important role in the course of chronic lung diseases. The presence of PA is considered crucial and has been associated with increased mortality in Cystic Fibrosis and bronchiectasis [23;24]. In COPD, some studies have demonstrated a high incidence during acute exacerbations [25;26] and have related the presence of PA in the sputum to higher mortality [6;27]. These findings are concordant with our cohort, where the prevalence of PA was 13% of hospitalized COPD patients and mortality among patients with PA was very high, reaching 18% at 90 days.

An important clinical concern related to PA is its fast acquisition of resistance to one or various antimicrobial agents [9;28]. The prevalence of PA-R is increasing, especially in nosocomial infections [8;29]. In our study, the prevalence of PA-R was around 13% of the whole cohort of COPD admitted patients and 66% of patients with PA in the sputum, which is higher than previous studies [16;25]. The administrations of corticosteroids and antibiotics in the previous 3 months were factors associated with the presence of PA-R. Prior antibiotic therapy, oral steroid use, prior hospitalization and FEV1 less than 35% have been related to the presence of PA in a culture of sputum at the time of exacerbation [25;30], but no to the presence of PA-R. This finding may have

important consequences in order to determine PA resistance patterns in these patients.

Recent studies in hospital-acquired infections have detected worse outcomes among those patients suffering PA-R. Micek et al demonstrated that in patients with PA nosocomial pneumonia, the presence of a MDR strain was associated with inappropriate initial antibiotic treatment and increased in-hospital mortality [15]. Different studies in hospitalized patients with PA bacteremia, most of them due to pneumonia [11;14], showed increased LOS and mortality among those with MDR PA isolation. In COPD patients, Montero et al [16] demonstrated in a case-control study that exacerbated COPD patients with MDR PA in the sputum had a higher long-term mortality compared to COPD patients with sensitive microorganisms isolated in the sputum. PA may colonize the respiratory tract of people with COPD, especially in those with severe disease [4;31]. Murphy et al [5] reported two distinct patterns of carriage of PA among COPD patients in a large prospective cohort; a short-term infection followed by clearance and a long-term persistence mostly due to mucoid strains. In addition, these authors showed a strong association between acquisition of a new strain of PA and the presence of an acute exacerbation of COPD. These findings could have an important significance and may potentially explain why our patients with PA-S had higher rates of mortality, but were less likely to persist in the sputum of appropriately treated patients. In addition, it also suggests that patients with PA-R may be more likely to have PA colonization for long periods of time, modulating the immune response and protecting them for poor clinical outcomes, despite the difficulties to fully

eradicate the bacteria by the use of appropriate antimicrobial agents. Further studies are needed to investigate this important clinical observation.

The key determinants of outcome in PA infection are likely to be the availability of effective antimicrobial therapy, and the virulence of the infecting microorganism. In the context of MDR PA, with the administration of inappropriate antibiotic therapy we may expect higher mortality. In this study, however, we hypothesized that if appropriate antibiotic therapy was used, patients with PA-R would have better outcomes because of the downregulation of virulence factors associated with chronic infection and the acquisition of antibiotic resistance. It is well described that acquisition of antibiotic resistance genes typically confers a fitness cost on bacteria in terms of reduced virulence [32]. In addition, antibiotic resistant is often associated with chronic infection, and it has been shown across multiple studies in cystic fibrosis that adaptation to chronic infection in the airway involves multiple gene alterations to reduce antigenicity, invasiveness and secretion of toxins. Indeed the “hallmark” of chronic PA infection, the formation of biofilms is intrinsically linked to the development of antibiotic resistance [33].

In this study, we found that the presence of PA-R was associated with lower 30- and 90-day mortality, where no differences regarding proper initial antibiotic therapy among groups were found. Furthermore, patients with PA-R had a trend of a higher rate of prior PA isolation and a higher persistence of PA after antibiotic treatment. These findings suggested that PA-R chronically colonized patients with severe COPD. The implications of these findings are therefore important for our understanding of PA infections in COPD. It appears that in contrast to common belief that PA-R is associated with higher virulence and

mortality, if patients are treated with appropriate antimicrobial therapy the reverse is true, and lower virulence in chronic strains results in improved patient outcomes. Limits among colonization and infection are still not clear and requires further studies to better elucidate.

Our study has several limitations. First, because the data were collected from a single academic center in Spain, the results might not be generalizable to other COPD patients admitted to other types of hospitals and other countries. Second, although it is larger that other studies that evaluated clinical outcomes of PA in exacerbated COPD patients [16;25-27], our sample size is small, especially for comparing MDR and not-MDR PAR. Third, we did not collected data on patients without PA in their sputum and it is not possible to compare risk factors and outcomes among patients with and without PA in their sputum. Fourth, the study was performed exclusively in hospitalized COPD patients, where PA isolation is more frequent than outpatients with COPD [34]. Fifth, although all patients included in the study had an acute episode, the isolation of PA in spontaneous sputum can either represent upper airway colonization or lower respiratory tract infection, which it is not possible to differentiate in these patients. And finally, it is not possible to exclude the role of bronchiectasis as a cofounder in the whole cohort.

In conclusion, we suggest that hospitalized COPD patients with an acute exacerbation and the isolation of PA in the sputum during the first 72 hours of admission have different clinical outcomes depending PA antimicrobial resistant patterns. AECOPD patients with PA-S have higher rates of short-term mortality compared to patients with PA-R, but lower rates of PA sputum persistence in

spite of an appropriate antimicrobial treatment. Additional studies are needed to understand the underlying mechanisms that are responsible for these findings.

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**FIGURE LEGENDS**

**Figure 1.-** Kaplan-Meier survival curves according to the presence of Resistant PA (PAR) vs Sensitive PA (PAS).

**Table 1**.- Patient demographics, clinical characteristics, comorbid conditions and prior treatments among COPD patients with PAS and PAR in sputum.

| **Variables** | **PA-S** (n=18) | **PA-R** (n=36) | **P value** |
|---|---|---|---|
| Age, years | 79 (SD 8.1) | 76 (SD 7,2) | 0.3 |
| Male gender | 16 (88%) | 32 (88%) | 0.9 |
| BMI (kg/m2) | 27.7 (SD 4.2) | 25.4 (SD 5) | 0.6 |
| **Comorbid conditions** | | | |
| Current smoker | 4 (22%) | 4 (11%) | 0.2 |
| Current alcohol user | 6 (33%) | 7 (19%) | 0.2 |
| Ischemic heart disease | 4 (22%) | 10 (27%) | 0.6 |
| Prior malignancy | 6 (33%) | 11 (30%) | 0.8 |
| Chronic kidney disease | 2 (11%) | 6 (16%) | 0.5 |
| Diabetes mellitus | 2 (11%) | 10 (27%) | 0.1 |
| Hypertension | 15 (83%) | 20 (55%) | 0.1 |
| Stroke | 2 (11%) | 2 (5%) | 0.4 |
| Bronchiectasis | 2 (11%) | 9 (25%) | 0.2 |
| **Functional status** | | | |
| $FEV_1$ (%) | 42 (SD 15) | 33 (SD17) | 0.6 |
| FVC (%) | 62.5 (SD 15,949) | 65,88 (SD 14,088) | 0.4 |
| Oxygen home treatment | 12 (66%) | 23 (63%) | 0.8 |
| Hospital admissions the previous year | 2.3 (SD 2.2) | 2.8 (SD 2.0) | 0.5 |
| **Current respiratory treatment** | | | |
| ICS use | 14 (77%) | 31 (86.1%) | 0.4 |
| LABA use | 16 (88%) | 35 (97.2%) | 0.2 |
| LAMA use | 17 (94.4%) | 34 (94.4%) | 0.9 |
| Roflumilast use | 2 (11%) | 6 (16%) | 0.5 |
| Chronic macrolide treatment | 2 (11%) | 5 (13%) | 0.7 |
| **Previous treatment (last 3 months)** | | | |

| | | | |
|---|---|---|---|
| SCS | 8 (44%) | 28 (77%) | **0.03** |
| Antibiotics | 7 (38%) | 28 (77%) | **0.01** |
| Antibiotics preceding admission | 2(11%) | 4(11%) | **1.0** |
| **Clinical signs** | | | |
| Fever (≥38º C) | 2 (11%) | 6 (16%) | 0.5 |
| Temperature | 36.2 (SD 0.9) | 36.2 (SD 0.8) | 0.3 |
| Sputum purulence | 15 (83%) | 24 (67%) | 0.3 |
| Anthonisen Criteria | 2.44 (SD 0.6) | 2.11 (SD 0.4) | 0.2 |
| **Laboratory tests** | | | |
| Leukocytes (U/mL) | 14360 (SD 13977) | 12698 (SD 6941) | 0.6 |
| pO2 (mmHg) | 55 (SD 14) | 63 (SD15) | 0.9 |
| pO2/FiO2 | 231.1 (SD 54.3) | 242.5 (SD 48.5) | 0.1 |
| pCO2 (mmHg) | 54 (SD 16) | 49 (SD 12) | 0.1 |
| **Previous admission** | | | |
| ≥ 2 Hospital admission/year | 7 (38%) | 11 (30%) | 0.6 |
| Healthcare admission/previous year | 2(11%) | 5 (14%) | 0.7 |
| ICU admission/previous year | 0(0%) | 1 (2.8%) | 0.4 |
| Number of Hospital admissions/previous year | 2.3 (SD 2.2) | 2.8 (SD 2.0) | 0.5 |
| Number of Healthcare admissions/previous year | 0.11 (SD 0.3) | 0.19 (SD 0.5) | 0.5 |

Data are presented as n (%) unless otherwise indicated.
$FEV_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; ICS; inhaled corticosteroids, LABA: long acting beta-agonist, LAMA: long acting muscarinic antagonist. SCS: Systemic Corticosteroids
ICU; Intensive Care Unit

Table 2.- Outcomes according PA resistance patterns in COPD exacerbations.

| | **PA S** (n=18) | **PA R** (n=36) | **P value** |
|---|---|---|---|
| 30-day mortality | 4 (22%) | 1 (2.8%) | **0.03** |
| 90-day mortality | 6 (33%) | 3 (8.3%) | **0.04** |
| Hospital LOS | 19.3 (SD28.6) | 12.9 (SD7.4) | **0.01** |
| Intensive care Unit admission | 3 (16%) | 2 (5.6%) | 0.1 |
| NIV | 5 (27%) | 7 (19%) | 0.5 |
| MV | 3 (16%) | 1 (2.7%) | 0.06 |
| Persistence 90-days | 4/8 (50%) | 25/30 (83%) | **0.01** |

Data are presented as n (%) unless otherwise indicated.
LOS: Length-of Stay; NIV; Non-invasive ventilation; MV: Mechanical Ventilation

**Table 3.** Patient demographics, clinical characteristics, comorbid conditions and prior treatments among COPD patients with PAR not-MDR and MDR in sputum.

| Variables | Not-MDR (n=17) | MDR (n=19) | p value |
|---|---|---|---|
| Age, years | 76.2 (SD 8.3) | 77.3 (SD 6.3) | 0.3 |
| Sex (male) | 15 (88%) | 17 (89%) | 0.9 |
| BMI (kg/m2) | 25.4 (SD 5.9) | 25.4 (SD 4.2) | 0.3 |
| **Comorbid conditions** | | | |
| Current smoker | 2 (11.8%) | 2 (10.5%) | 0.9 |
| Current alcohol user | 2 (12.5%) | 5 (26.3%) | 0.3 |
| Ischemic heart disease | 4 (23.5%) | 6 (31.6%) | 0.51 |
| Prior malignancy | 8 (47.1%) | 3 (15.8%) | **0.04** |
| Chronic kidney disease | 3 (17.6%) | 3 (15.8%) | 0.08 |
| Diabetes mellitus | 6 (35.3%) | 4 (21.1%) | 0.3 |
| Hypertension | 8 (47%) | 12 (63.2%) | 0.4 |
| Stroke | 1 (5.9%) | 1 (5.3%) | 0.9 |
| Bronchiectasis | 6 (35.3%) | 3 (16%) | 0.3 |
| **Functional status** | | | |
| $FEV_1$ (%) | 34.8 (SD 18.7) | 32.5 (SD 16.0) | 0.5 |
| FVC (%) | 62 (SD 14.9) | 63 (SD 17.2) | 0.3 |
| Oxygen home treatment | 9 (52.9%) | 14 (73.7%) | 0.1 |
| **Current respiratory treatment** | | | |
| ICS use | 14 (82%) | 17 (89%) | 0.5 |
| LABA use | 17 (100%) | 18 (94%) | 0.3 |
| LAMA use | 16 (94%) | 18 (94%) | 0.9 |
| Roflumilast use | 3 (17.6%) | 3 (15.8%) | 0.8 |
| Chronic macrolide treatment | 2 (11.8%) | 3 (15.8%) | 0.7 |
| **Previous treatment (last 3 months)** | | | |
| SCS | 13 (76.5%) | 15 (78.9%) | 0.8 |
| Antibiotics | 13 (76.5%) | 15 (78.9%) | 0.8 |

| | | | |
|---|---|---|---|
| **Clinical signs** | | | |
| Fever (≥38º C) | 1 (5.9%) | 5 (26.3%) | 0.1 |
| Temperature | 36,282 (SD 0.77) | 36,621 (SD 1.03) | 0.2 |
| **Laboratory tests** | | | |
| Leukocytes (U/mL) | 13011 (SD 7420) | 12418 (SD 6676) | 0.5 |
| pO2 (mmHg) | 64.2 (SD 12.4) | 62.6 (SD 18.36) | 0.2 |
| pO2/FiO2 | 256.7 (SD 58.6) | 230.9 (SD 36.4) | 0.3 |
| pCO2 (mmHg) | 50.4 (SD 11.4) | 49 (SD 12.9) | 0.8 |
| **Previous admission** | | | |
| ≥ 2 Hospital admission/year | 5 (38.5%) | 6 (35.3) | 0.8 |
| Number of Hospital admissions/ previous year | 3 (SD 2.7) | 2.6 (SD 1.2) | 0.2 |

Data are presented as n (%) unless otherwise indicated.
$FEV_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; ICS; inhaled corticosteroids, LABA: long acting beta-agonist, LAMA: long acting muscarinic antagonist. SCS: Systemic Corticosteroids

**Table 4**. Outcomes according the presence of multi-drug resistance (MDR) in COPD patients with PAR.

| | **Not-MDR** | **MDR** | **p value** |
|---|---|---|---|
| 30-day mortality | 1 (5.9%) | 0% | 0.3 |
| 90-day mortality | 3 (17.6%) | 0% | 0.05 |
| Hospital LOS | 13.1 (SD 6.8) | 12.8 (SD 8) | 0.6 |
| Intensive care Unit admission | 1 (5.9%) | 1 (5.3%) | 0.9 |
| NIV | 5 (31.3%) | 2 (10.5%) | 0.1 |
| MV | 0% | 1 (5.3%) | 0.3 |
| Persistence 90-days | 11/14 (75%) | 14/16 (87%) | 0.7 |

Data are presented as n (%) unless otherwise indicated.

LOS: Length-of Stay; NIV; Non-invasive mechanical ventilation; MV: Mechanical Ventilation

Reference List


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